

Complete Summary

GUIDELINE TITLE

Genetic testing for hereditary pancreatitis: guidelines for indications, counselling, consent and privacy issues.

BIBLIOGRAPHIC SOURCE(S)

Ellis I, Lerch MM, Whitcomb DC. Genetic testing for hereditary pancreatitis: guidelines for indications, counselling, consent and privacy issues. *Pancreatology* 2001;1(5): 405-15. [50 references] [PubMed](#)

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SCOPE

DISEASE/CONDITION(S)

Hereditary pancreatitis

GUIDELINE CATEGORY

Counseling
 Diagnosis

CLINICAL SPECIALTY

Gastroenterology
 Medical Genetics
 Obstetrics and Gynecology
 Pediatrics

INTENDED USERS

Advanced Practice Nurses
Allied Health Personnel
Health Care Providers
Nurses
Physicians

GUIDELINE OBJECTIVE(S)

To recommend proper ethical principles for service-based testing of hereditary pancreatitis

TARGET POPULATION

- Patients diagnosed with pancreatitis that has raised the suspicion of hereditary pancreatitis
- Persons suspected to be at risk for hereditary pancreatitis
- Pregnant females who are at risk for having a child with hereditary pancreatitis

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnostic molecular genetic testing for hereditary pancreatitis, specifically, cationic trypsinogen (PRSS1) mutation analysis along with informed consent and counselling

MAJOR OUTCOMES CONSIDERED

Not stated

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Not stated

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Expert Consensus (Committee)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Not applicable

METHODS USED TO ANALYZE THE EVIDENCE

Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Expert Consensus (Consensus Development Conference)

DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

During the consensus conference, Charles Ulrich II, MD, from the University of Cincinnati, Cincinnati, Ohio, USA, presented cost analysis and other practical limitations associated with the attempt to screen patients with hereditary pancreatic cancer (HPC) or hereditary pancreatitis. The pathophysiology of hereditary pancreatitis was reviewed, including the epidemiological data suggesting a risk of pancreatic cancer approaching 40% by the age of 70 years. Although the risk is high, there is uncertainty as to the best way to follow these patients. Based on current estimates, approximately seven pancreatic cancers will develop or be diagnosed among the population of hereditary pancreatitis patients over the age of 40 years (n = 250). If screening were expanded to include serum and pancreatic juice markers and imaging studies (computed tomography [CT], endoscopic ultrasound [EUS] and endoscopic retrograde cholangiopancreatography [ERCP]), the research cost would be USD 2,032 per person per year, with a total cost exceeding USD 2,540,000 (USD 365,857 per tumor detected). EUS alone, with banked markers, would reduce this cost to USD 164,285 per tumor detected, but the impact of this detection on survival is unknown.

Source (see also the "Companion Document" field): Whitcomb DC, Ulrich CD, Lerch MM, Durie P, Neoptolemos JP, Maisonneuve P, Lowenfels AB. Third International Symposium on Inherited Diseases of the Pancreas. *Pancreatology* 2001;1(5):423-31.

METHOD OF GUIDELINE VALIDATION

Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Not stated

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The Decision to Offer Diagnostic Molecular Genetic Testing

The guideline developers are aware that with the introduction of any new test there is a desire to 'try it out'. They set out specific indications for the decision to offer diagnostic molecular genetic testing for hereditary pancreatitis (HP). Outside of defined Ethics Committee Approved Research Protocols, the indication for cationic trypsinogen (PRSS1) gene mutation analysis in a symptomatic patient should be any of the following:

1. Recurrent (2 or more separate, documented episodes with hyper-amylasaemia) attacks of acute pancreatitis for which there is no explanation (anatomical anomalies, ampullary or main pancreatic strictures, trauma, viral infection, gallstones, alcohol, drugs, hyperlipidaemia, etc.)

OR

2. Unexplained (idiopathic) chronic pancreatitis

OR

3. A family history of pancreatitis in a first-degree (parent, sib, child), or second-degree (aunt, uncle, grandparent) relative

OR

4. An unexplained episode of documented pancreatitis occurring in a child that has required hospitalization, and where there is significant concern that HP should be excluded (see 'The Genetic Testing of Children,' below)

OR

5. For patients with pancreatitis eligible for an Ethics Committee Approved Research Protocol

The above criteria focus on patients who have already manifested pancreatitis that has raised the clinical suspicion of HP. The authors are aware that the incomplete penetrance, variability of expression and the description of a new mutation of PRSS1 may obscure a positive family history. Clearly, there must be clinical freedom to arrange PRSS1 molecular genetic testing in 'grey' areas whilst guarding against a screen-all approach.

Pre-Test Hereditary Pancreatitis Information Prior to Diagnostic PRSS1 Molecular Genetic Testing

The detail into which any referring clinician goes with the following points will vary from setting to setting. It cannot easily be prescribed, but a pre-test information sheet (as can be downloaded from www.liv.ac.uk/surgery/coneuropac.htm, www.mmpsg.org, and www.pancreas.org in English, and from www.pancreas.de in German) given to the patient after a clinic discussion is one approach. The guideline developers believe that formal specialist genetic counselling is not required before the diagnostic genetic testing of a symptomatic adult, provided the nine pre-requisite points listed below have been covered. The guideline developers now support the offer of molecular genetic testing for HP by paediatricians, gastroenterologists, and pancreatic surgeons in routine clinical practice and outside of research studies. By opening what has been previously termed a 'pancreatic Pandora's box,' the guideline developers trust that other clinicians will use the test with care, after adequate patient preparation. The guideline developers suggest that informed consent is documented before the test and that detailed pre-test information has been given (consent forms are available from www.liv.ac.uk/surgery/coneuropac.htm, www.mmpsg.org and www.pancreas.org in English and from www.pancreas.de in German). Outside of a research study, as a minimum, the following steps should be covered in a service testing setting:

1. Why the test has been suggested and obtaining documented informed consent.
2. The implications of finding an HP-related mutation in the PRSS1 gene for the health and medical care of that patient.
3. How the genetic test result will be communicated to the patient, and who else will be informed of their result.
4. The availability of genetic counselling after the test result is known.
5. Apart from informing the patient, it would be usual practice for that laboratory result to also go to the clinician that has requested that test, other involved pancreatic specialists, and to the family doctor if appropriate.
6. The pancreatic cancer risk and the possible adverse health and life insurance and employment consequences for the patient (if not safeguarded against by national legislation).
7. The implications of a positive genetic test result for the patient's relatives.
8. Testing of the sample in an approved health service-funded or commercial molecular genetics testing laboratory with appropriate quality control standards.
9. Finding out whether the patient's test sample may then be used for any research project, and by what (anonymous) route this will occur.

Genetic Information Following a Positive Hereditary Pancreatitis Molecular Genetic Test Result

Providing a patient has been adequately prepared before their HP molecular genetic test, they should not be surprised by a positive test result, or by the implications when they are then explained to him/her. Should an HP mutation be found, good-quality genetic counselling from a recognized specialist genetic counselling service must then be offered to discuss the following points in more detail:

1. What the test result is, in terms of which gene mutation has been found, preferably in written form.
2. A description of the (autosomal) mode of inheritance and incomplete penetrance, and an emphasis on the variability of expression in lay terms that are easily understood by the patient and their family.
3. That the disease course and severity cannot be easily predicted, but that chronic pancreatitis, pancreatic exocrine and endocrine insufficiency are likely complications.
4. That the lifetime pancreatic cancer risk is estimated to be approximately 40% (Lowenfels et al., 1993, 1997; Howes et al., 2000).
5. What current management exists for pancreatic follow-up and pancreatic cancer risk surveillance.
6. The risks to relatives of inheriting this HP gene mutation, and their risks of developing pancreatitis.
7. A plan for the patient to inform their family of their test result, and the options for pancreatic investigation, genetic counselling and, if appropriate, genetic testing.
8. The patient should be encouraged, but not coerced, into telling their at-risk relatives.
9. What further research is available in this and related areas that the patient might be interested in joining.

These points focus on the genetic aspects of a test result. Clearly, the discussion will also cover many general pancreatic and surgical issues. Ideally, the patient should be seen within a multi-disciplinary clinic that can address many of these issues with a clear, coherent and consistent management plan.

Predictive Genetic Testing for Hereditary Pancreatitis

The predictive (pre-symptomatic) testing of unaffected relatives raises complex and competing issues. This is referred to specifically here and in detail. There is the desire to reassure unaffected relatives that they are indeed not gene carriers and not liable to develop HP or to pass it on. However, gene carriers who are young are still liable to present with their first episode of acute pancreatitis. This raises the question of testing children and the issues of protecting their autonomy until an age when they can give fully informed consent for themselves. Would a ten year old found to be an HP mutation carrier thank their parents if they later find difficulties with life or health insurance or in gaining employment when they actually remain symptom free? The balance shifts in favour of predictive testing if insurance issues can be safeguarded against, as has been done by the legislature in Germany. If effective interventions for HP mutation carriers are developed that protect against episodes of acute pancreatitis or the development of chronic pancreatitis or pancreatic cancer, then the balance will also swing more towards advocating predictive testing.

In the meantime, it is essential that careful and specialized genetic counselling is offered to all unaffected adults who are contemplating predictive genetic testing for HP. This group is especially vulnerable to the unwelcome and unexpected consequences of molecular genetic testing for HP. Service-based predictive testing is only suitable for the first-degree relatives of an HP patient who carries an already defined HP cationic trypsinogen gene (PRSS1) mutation that has an accepted clinical phenotype. Predictive genetic testing should only be offered by a

recognized service with adequate pre-test counselling, post-test support and clinical follow-up. The steps involved should include the following:

1. The person must have a first-degree relative with a defined HP gene mutation.
2. The person should be over 16 years of age and able to make an independent and fully informed decision. Although in some countries a parental request for genetic testing of an underage child cannot legally be declined, the above issues should be discussed with the parents in detail and the child's preferences should be taken into account.
3. Ideally, there should be a consistently stated (over at least three months since first contact) request for predictive testing.
4. The person should understand the (autosomal dominant) mode of inheritance and the incomplete penetrance of HP mutations.
5. There should have been a discussion with the person on the possible implications of finding they are an HP mutation carrier on their own health and whether this will lead to increased anxiety and possible stigmatization, for example.
6. It should be emphasized that if they are found to be an HP mutation carrier they cannot predict their own disease severity by comparison with their affected relatives.
7. The person should be informed that they are likely (80% gene penetrance) to have attacks of acute pancreatitis (Whitcomb et al., 1996). Current evidence indicates that if a person remains symptom free until the age of 20, there is about a 25% residual risk, and by the age of 30 years, a 10% residual risk of still manifesting HP and its attendant complications (Ellis et al., 2000).
8. The person should be informed that if they manifest attacks of pancreatitis, they are likely to go on to develop chronic pancreatitis and possibly pancreatic exocrine and endocrine insufficiency and will have a lifetime risk of pancreatic cancer estimated at over 40% (Lowenfels et al., 1993, 1997; Howes et al., 2000).
9. The current management for pancreatic follow-up and pancreatic cancer risk surveillance should be discussed.
10. It should be stated that if they do carry an HP mutation, there is about a 20% chance that they will remain symptom free with normal pancreatic function throughout their life and with no added risk of developing pancreatic cancer.
11. The person should be informed that there are possible adverse health and life insurance and employment consequences for an HP mutation carrier if these are not safeguarded against by national legislation.
12. The person should be told that if they decide to proceed with predictive genetic testing, that they must sign a consent form and then attend in person to receive their test result, i.e. that it will not be telephoned or posted to them.
13. The person should be informed of the risks to their relatives of also carrying this HP gene mutation, and of their risks of developing pancreatitis.
14. Whilst there are likely to be children at risk as a result of a positive genetic predictive test, the guideline developers would discourage the offer of predictive testing to unaffected young people (see 'The Genetic Testing of Children,' below).
15. Discussion should take place regarding who else will be informed of their result, and who in their family they plan to tell.
16. It should be discussed whether their test sample may then be used for any research project.

17. If they do carry an HP mutation, the person should be informed of what further research is available in this and related areas that they might be interested in joining.
18. The person should agree to a scheme for pancreatic follow-up if the genetic test result is positive.
19. The person should also agree that they will come in person to receive their predictive test result as it will not be given out by telephone, by letter, or to another person.
20. Arrangements should be made for the molecular genetic testing of their predictive test sample in an approved health service-funded or commercial molecular genetics testing laboratory with appropriate quality control standards.

The Genetic Testing of Children

The guideline developers believe that children present special difficulties in the area of molecular genetic testing. Ill-conceived plans to screen children for HP mutations may have harmful psychological and practical consequences, as described above. This applies particularly to predictive testing, which can seldom be justified under the age of 16 years in the absence of a clinically proven intervention strategy. Children may need to be protected from both medical and indeed parental 'paternalism'. Certainly, individual and parental views must be taken into account when there are strong feelings 'to know'. Anxious parents should be informed that genetic testing cannot predict the age of onset or the severity of the condition.

The age of 16 is somewhat arbitrary, but it is chosen as a watershed age. It will vary from family to family and from one culture to another. After the age of 12, the guideline developers believe that a child can begin to contribute to the decision-making process, and should certainly be included. Only by their 'mid-teens' has the person developed sufficiently to understand the competing and lifelong implications of any decision. Before that stage, the guideline developers would wish to postpone any decision until such time as that young person's autonomy can be protected. In most cases, the parents will be acting in the best interests of their child. Lifestyle modification is no reason to test children; advice to avoid alcohol use and smoking can be given to all at-risk children as well as children in the general population. Families with at-risk children are aware of potential HP symptoms, and it is emphasized that genetic testing can be performed if their child becomes symptomatic. Parents are encouraged to return for genetic advice when their children are older or become symptomatic. Such decision making should be shared with a recognized genetic counselling service experienced in dealing with a range of genetic and predictive testing issues for families. This remains an area of individual judgement, influenced by local practice and culture. The phrase, 'best interests of the patient' can be invoked here to guide decision making.

The diagnostic testing of an affected child is more straightforward. If a child of any age has presented with a well-documented episode of pancreatitis of unknown aetiology, then clearly HP is part of the differential diagnosis that needs to be excluded. The guideline developers believe that these are the indications for the molecular testing of a child (under the age of 16 years) for HP:

1. An episode of documented pancreatitis of unknown aetiology and severe enough to require hospitalization

OR
2. Two or more documented episodes of pancreatitis of unknown aetiology

OR
3. An episode of documented pancreatitis occurring in a child where a relative is known to carry an HP mutation

OR
4. A child with recurrent abdominal pain of unknown aetiology where the diagnosis of HP is a distinct clinical possibility

OR
5. Chronic pancreatitis of unknown aetiology, where the diagnosis of HP is a distinct clinical possibility

The guideline developers are concerned that the availability of molecular genetic testing for PRSS1 mutations should not be used in general paediatric practice to screen all children with abdominal pain of uncertain aetiology and without evidence of pancreatitis.

Prenatal Testing for Hereditary Pancreatitis

The guideline developers believe that the option of prenatal diagnosis should be discussed as part of the general discussion of the genetic and clinical issues raised by HP. Assuming a culture of non-directive, non-judgemental genetic counselling that encourages decision making by the family, clinicians cannot decide for or against this by themselves. It may be fair to say that members of a multi-disciplinary clinical and molecular laboratory team managing such patients may have reservations about the widespread offer of prenatal testing and ultimately the possibility of termination of pregnancy for HP. The reasons for this, and what should be discussed with a couple enquiring about prenatal testing, involve the following points:

1. Research into HP is being actively pursued. There may be cautious optimism that interventions may be available in ten years time that will offer more than the current supportive approaches.
2. The family may have first-hand experience of HP and any decision that they ultimately make should be well informed and supported by the multi-disciplinary team (gastroenterology, pancreatic surgery, genetics, obstetrics) involved in their care.
3. Continuing an 'affected' pregnancy would amount to having had a predictive test on the unborn child. The guideline developers would wish to avoid this if possible.

4. If the family are requesting prenatal testing, their reasons may be influenced by a severe case in their family and perfectly understandable concerns about the eventual development of chronic pancreatitis and the 40% lifetime risk of pancreatic cancer.
5. The condition is variable, with incomplete penetrance. The genotype does not predict the phenotype. If a pregnancy is terminated there would be no way (currently) of telling if that pregnancy would have resulted in a child that would have been mildly or more severely affected or even unaffected.
6. It should be pointed out that research protocols are being developed by the European Registry of Hereditary Pancreatitis and Familial Pancreatic Cancer (EUROPAC) for screening patients with HP who are over the age of 40 and at risk of developing pancreatic cancer.
7. Despite any reservations that the guideline developers have, they believe that they cannot be so prescriptive as to refuse molecular genetic testing in an age of patient autonomy and informed consent. Otherwise they risk medical paternalism.

The guideline developers emphasize again that this is an area where lengthy and specialized genetic counselling would be required.

Storing a DNA Sample

The approach to DNA storage will vary from centre to centre and may range from very open access to those DNA laboratories that are tightly regulated. The latter may have specific protocols and require documented informed consent. The position will vary from country to country, and even from laboratory to laboratory. The position in the United Kingdom, the position in Europe, the position in the United States, and the International Consensus are described in the original guideline document.

The Transfer of Samples and Information between Service and Research Testing

The interface between service and research testing programmes is complex and potentially fraught with difficulties. Under no circumstances should DNA samples be taken casually from unaffected subjects. A genetic test result may inadvertently be disclosed, with dire consequences for the individual, his/her future, children and indeed the researchers. Technically, it can be viewed as an assault. Samples can be taken on the basis of non-disclosure of research results. These samples must be anonymous or the samples carefully coded so as to protect the identity of the individuals and to guard against the inadvertent release of unwanted genetic information. It is imperative that such samples obtained for research purposes are never used for clinical management and are never inadvertently disclosed. In this way, there should be no adverse insurance or psychological consequences. Figure 1 in the original guideline document presents a suggested model for the separate handling of service and research samples, and the possible contact points between these routes.

CLINICAL ALGORITHM(S)

A suggested model for handling service and research samples is provided in the original guideline document.

EVIDENCE SUPPORTING THE RECOMMENDATIONS

REFERENCES SUPPORTING THE RECOMMENDATIONS

[References open in a new window](#)

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is not specifically stated for each recommendation.

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Appropriate and ethical management of genetic testing for hereditary pancreatitis

POTENTIAL HARMS

Not stated

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

The guideline developers built their guidelines upon the desire to maximize patient autonomy in decision-making, ensuring fully informed consent and respect for individual choice and non-directive and non-judgmental genetic counselling.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Staying Healthy

IOM DOMAIN

Effectiveness
Patient-centeredness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Ellis I, Lerch MM, Whitcomb DC. Genetic testing for hereditary pancreatitis: guidelines for indications, counselling, consent and privacy issues. *Pancreatology* 2001;1(5): 405-15. [50 references] [PubMed](#)

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

2001

GUIDELINE DEVELOPER(S)

European Registry of Hereditary Pancreatic Diseases - Disease Specific Society
International Association of Pancreatology - Disease Specific Society
Midwest Multi-Center Pancreatic Study Group - Disease Specific Society

SOURCE(S) OF FUNDING

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GUIDELINE COMMITTEE

Not stated

COMPOSITION OF GROUP THAT AUTHORED THE GUIDELINE

The following authors contributed to the guideline development process at the Third International Symposium on Inherited Diseases of the Pancreas, Milan, Italy, April 5-7, 2001 (in alphabetical order): B.E. Argent; D. Bartsch; R.H. Bell; M.D. Bishop; T.A. Brentnall; G.R. Chandak; J.M. Chen; M. Cipolli; J.A. Cohn; D.L. Conwell; J.E. Creighton; M. Delhaye; A. Demols; E.P. DiMagno; J.A. Dodge; P. Durie; D. Easton; I. Ellis; L. Ellis; C. Ferec; S. D. Freedman; H. Friess; K.J. Gaskin; L. Graf; W. Greenhalf; L. Guarner; N.R. Howes; S. Intini; M. Kaori; V. Keim; E. Kopras; R. Laugier; N. Lemoine; M.M. Lerch; A.B. Lowenfels; H.T. Lynch; P. Maisonneuve; N. Malats; J. Martinek; G. Mastella; X. Molero; R. Mountford; J.P.

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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

This is the current release of the guideline.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from [Pancreatology](#), a Karger publication.

Print copies: Reprints available by request from Dr. Ian Ellis, FRCP, BSc; Department of Clinical Genetics, Alder Hey Children's Hospital; Eaton Road, Liverpool L12 2AP England; Tel. +44 151 252 5905, Fax +44 151 252 5951; E-Mail Ian.Ellis@VRcade.net.

AVAILABILITY OF COMPANION DOCUMENTS

The following is available:

- Whitcomb DC, Ulrich CD, Lerch MM, Durie P, Neoptolemos JP, Maisonneuve P, Lowenfels AB. Third International Symposium on Inherited Diseases of the Pancreas. *Pancreatology* 2001;1(5):423-31.

Electronic copies: Available in Portable Document Format (PDF) from [Pancreatology](#), a Karger publication.

PATIENT RESOURCES

None available

NGC STATUS

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The logo for FIRSTGOV, with "FIRST" in blue and "GOV" in red, and a small red star above the "I".

